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LETTER TO THE EDITORS

Pregnant woman saved with liver transplantation from acute liver failure due to hepatitis E virus

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Dear Sirs,

Hepatitis E virus (HEV), the only virus within the genus *Hepevirus* and the family *Hepeviridae* [1], is one of the major causes of enterically transmitted hepatitis in many developing countries. Industrialized countries were considered nonendemic, but an increasing number of nontravel-associated cases of HEV infection have been reported in recent years, particularly in Europe [2,3].

While acute HEV infection is considered a self-limiting liver disease, with a 0.2–4% mortality rate [4], it sometimes progresses to acute liver failure (ALF), especially in pregnant women and in patients with pre-existing chronic liver diseases. In particular, the hepatitis E-induced mortality rate during pregnancy ranges from 15% to 25% [4–6] when the infection is contracted in the third trimester of pregnancy.

Although it is not understood why HEV infection is associated with severe liver injury in pregnant women, ALF during pregnancy is known to be associated with a higher viral load of HEV, compared with those of acute hepatitis [7,8]. Bose *et al.* [8] reported that the severe course in pregnant women is related to a reduction in the expression of progesterone-receptor, which led to a predominance of T-helper type 1 lymphocytes. This immunologic shift results in an exuberant cytotoxic T-cell reaction resulting in foetal and maternal injury. Orthotopic liver transplantation (OLT) is a treatment option for patients with ALF. To the best of our knowledge, OLT has never been performed before for HEV-induced ALF.

A 28-year-old Asian pregnant woman was admitted in urgency in the obstetric-gynaecological unit due to persistent vomiting associated with abdominal pain and general malaise. The patient had returned from her country of origin in Southeast Asia 2 weeks before, after a 1-month stay. The patient had no history of prior liver disease or drug intake.

Vital signs were within normal limits, as well as the gynaecological examination. Cardiotocography and the trans-vaginal and abdominal sonograms were normal. On physical examination, the patient was alert, oriented, with mildly impaired speech and scleral jaundice. The abdomen was slightly tender, with no signs of peritoneal reaction or ascites; the liver was not enlarged. Blood analysis demonstrated the following abnormalities: white blood count 15.7×10^3/mmc, international normalized ratio (INR) 4.69, glucose 58 mg/dl, total/conjugate bilirubin (TB/CB) 19.01/13.48 mg/dl, aspartate aminotransferase (AST) 529 U/l, alanine aminotrasferase (ALT) 848 U/l, ammonium 74 μM, lactate dehydrogenase 285 U/l and lactic acid 6.9 mM. The calculated Model for End-Stage Liver Disease (MELD) score was 33.

The patient was then moved to the intensive care unit (ICU), where was started a treatment with high dosage *N*-acetylcysteine and fresh frozen plasma. Major causes of acute hepatitis, including hepatitis A, B, C, cytomegalovirus, Epstein–Barr, herpes simplex and varicella zoster viruses were ruled out using serological and/or molecular testing. Gynaecological causes of hepatic function impairment (i.e. HELLP syndrome, intrahepatic cholestasis and acute fatty liver of pregnancy) were ruled out, as well as hepatic masses and portal or hepatic veins thrombosis. Due to the recent trip in an endemic area, a blood sample to test HEV IgG and IgM as well as HEV-RNA was sent to the Virology Unit of the University of Parma.

According to the King's College Hospital criteria for non-acetaminophen-induced ALF, OLT is indicated if three on the five considered parameters are satisfied (unfavourable aetiology of the disease, age of the patient <10 or >40 years, duration of jaundice before the onset of hepatic encephalopathy >7 days, INR > 3.5, TB > 17.5 mg/dl), as death occurred in 97% of the cases in absence of OLT [9]. According to this guideline, the patient was subsequently listed for emergency OLT for unknown acute hepatic necrosis.

After the correction of the coagulation, the patient underwent emergency caesarean section. The baby, a 1.7-kg boy, was transferred in the Neonatal ICU for the supportive cares. After delivery, anti-HEV empirical treatment with ribavirin (RBV) 15 mg/kg/day was started. The day after the diagnosis of acute hepatitis E was confirmed by the detection of anti-HEV (both IgG and IgM) in the serum

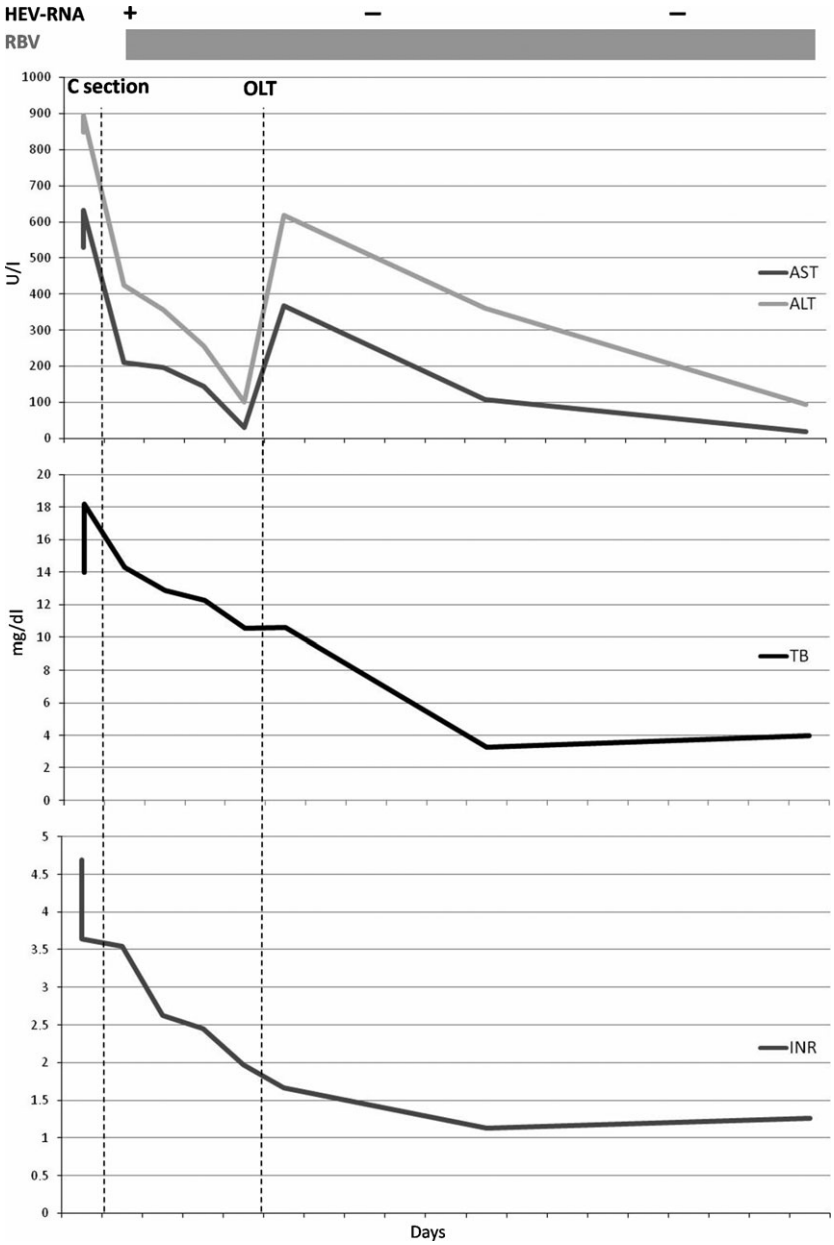

Figure 1 Evolution of liver biological tests and Hepatitis E virus (HEV)-RNA of the patient. RBV, ribavirin; INR, international normalized ratio; TB, Total Bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

(HEV ELISA – enzyme-linked immunosorbent assay – KIT and HEV IgM ELISA 3.0; MP Diagnostics Asia Pacific Pte Ldt, Singapore) and the detection of HEV-RNA in the plasma analysed by a qualitative Retro transcriptase-real-time polymerase chain reaction (RT-Real time PCR) (Real time Star HEV RT-PCR 1.0; Altona diagnostics, GmbH, Hamburg, Germany). Unfortunately, genotype determination was not possible in our laboratory.

In the following days, the patient neurological status worsened; neurological examination revealed stupor without signs of focal neurological deficits. The electroencephalogram confirmed the presence of diffuse alterations caused by the metabolic encephalopathy. The Glasgow Coma Scale was 5. Serum chemistry results were stable. Five days after delivery, the patient underwent OLT. The histological examination of the native liver showed diffuse confluent necrosis associated with marked cholestasis. The immunosuppression was based on tacrolimus and steroids.

RBV treatment was stopped the 14th postoperative day, after two negative determinations of HEV-RNA. One

further determination of HEV-RNA, made 7 days after RBV suspension, was still negative, while both IgG and IgM remained positive. The evolution of liver biological tests and HEV-RNA is shown in Figure 1.

The patient was discharged after 34 days from OLT. The baby was discharged 2 months after birth without signs or symptoms of acute hepatitis E infection. The infant was seropositive for anti-HEV IgG derived from maternal passive immunity, while plasma anti-HEV IgM and HEV-RNA were negative.

Twelve months after OLT, both the patient and her baby are in good clinical conditions, with normal blood tests.

Although we cannot draw a conclusion from a single case, three take-home messages could be elicited from our case-report: (i) in case of hepatic function impairment during pregnancy, HEV serology determination should be routinely performed, even in nonendemic areas; (ii) RBV treatment should be started as soon as possible to decrease viral replication, even in HEV infection suspicion; (iii) OLT is a feasible and curative procedure in case of HEV-induced ALF.

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References

1. Emerson SU, Anderson D, Arankalle AV, *et al.* Hepevirus. In: Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball LA, eds. *Virus Taxonomy. The Eighth Report of the International Committee on Taxonomy of Viruses*. London: Elsevier/Academic Press, 2004; 851.
2. Lewis HC, Wichmann O, Duizer E. Transmission routes and risk factors for autochthonous hepatitis E virus infection in Europe: a systematic review. *Epidemiol Infect* 2010; **138**: 145.
3. Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. *N Engl J Med* 2012; **367**: 1237.
4. Kamar N, Bendall R, Legrand-Abravanel F, *et al.* Hepatitis E. *Lancet* 2012; **379**: 2477.
5. Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI. Incidence and severity of viral hepatitis in pregnancy. *Am J Med* 1981; **70**: 252.
6. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med* 2007; **147**: 28.
7. Kar P, Jilani N, Husain SA, *et al.* Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? *Am J Gastroenterol* 2008; **103**: 2495.
8. Bose PD, Das BC, Kumar A, Gondal R, Kumar D, Kar P. High viral load and deregulation of the progesterone receptor signalling pathway: association with hepatitis E-related poor pregnancy outcome. *J Hepatol* 2011; **54**: 1107.
9. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439.