Case Report

Hepatitis E: An Underdiagnosed, Emerging Infection in Nonendemic Regions

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Abstract

Although hepatitis E virus (HEV) is the primary cause of enterically transmitted acute hepatitis and jaundice in developing countries, locally acquired HEV infections are increasing in nonendemic countries. As such, HEV is emerging as an underdiagnosed cause of infection. This report describes three clinically variable cases of HEV infection with unusual clinical presentations. These cases highlight the fact that HEV should be considered in the differential diagnosis of patients with unexplained hepatitis (acute or chronic) with or without extrahepatic manifestations. HEV should also be considered in patients with persistently elevated liver enzymes who have not travelled to known HEV-endemic regions. Lack of knowledge among physicians and an absence of standardized diagnostic tests may result in increased morbidity and mortality from HEV infection.

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Case reports

Patient 1

In December 2009, a 32-year-old Caucasian woman was diagnosed with acute myeloid leukemia [t(11;19)]. She had no history of recent travel, contact with animals, or consumption of venison, liver sausage, or offal. She received a blood transfusion prior to undergoing consecutive cycles of chemotherapy. In February 2010, she underwent hematopoietic stem cell transplantation with cells obtained from her brother. A standard screening protocol performed prior to the transplantation showed she was seropositive for HSV, CMV, varicella zoster virus (VZV), EBV, and T. gondii. Further virologic investigation revealed vaccine-derived immunity to HBV, but no evidence of HAV, HCV, or HIV. One month post-transplantation, in March 2010, CMV reactivated and was treated with consecutive antiviral agents (valacyclovir, foscamet, ganciclovir, and cidofovir). In May 2010, pathologic laboratory values were obtained for alanine aminotransferase (ALT; 544 IU/L), aspartate aminotransferase (259 IU/L), and gamma-glutamyltransferase (GGT; 92 IU/L). Findings from serologic investigation revealed vaccine-derived immunity to HBV, but no evidence of HAV, HCV, or HIV. One month post-transplantation, in March 2010, CMV reactivated and was treated with consecutive antiviral agents (valacyclovir, foscamet, ganciclovir, and cidofovir).

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Liver function tests remained abnormal, and in November 2010, a serum test for HEV RNA was conducted, revealing a high viral load (>5×10^5 copies/mL). Thus, a diagnosis of HEV infection (genotype 3f) was made, and the patient was treated with ribavirin monotherapy. Serologic HEV testing (RecomWell Hepatitis IgG/IgM; Mikrogen GmbH, Neuried, Germany) remained negative. Although no serum samples were available to evaluate pretransplant serostatus, the hematopoietic stem cell donor was HEV-seronegative. The HEV viraemia remained stable (5×10^6 copies/mL) for several months. In February 2011, Aspergillus pneumonia with pleural effusion appeared, without hepatic involvement, which was treated with caspofungin plus amphotericin B. One week later, the patient became extremely confused and suffered from dizziness and reduced consciousness. Examination of a plasma sample showed 2,565 copies/mL of adenovirus in addition to the persistent, high HEV viral load (5×10^5 copies/mL), and a sample of cerebral spinal fluid was positive for HEV RNA (3,700 copies/mL); CMV, adenovirus, EBV, and Toxoplasma were excluded.

The patient died in March 2011 due to multiple organ failure. Based on the chronic (>3 months), high-level detection of HEV RNA and no reported recent travel to endemic areas, an autochthonous, chronic HEV infection was most likely. An alternative origin of infection, such as the ingestion of contaminated food during the post-transplant period or transplantation of contaminated cells or blood products could not fully be excluded. Furthermore, no remaining stem cell preparation (prepared in an external laboratory) could be tested for the presence of HEV RNA.

**Patient 2**

In March 2013, a 62-year-old Bulgarian man was admitted with a provisional diagnosis of acute hepatitis based on a preexisting chronic HBV infection (inactive HBV carrier state: positive for HB surface antigen, core antibody, and envelope antibody; negative for HB envelope antigen and surface antibody with existing cirrhosis and ascites). One day prior to admission, the patient suffered from an acute onset of progressive, worsening upper abdominal discomfort, frequent episodes of diarrhea (2–3 times/day), loss of appetite, and fulminant jaundice without systemic symptoms. Laboratory results revealed elevated levels of aspartate aminotransferase (2,452 IU/L), ALT (1,161 IU/L), and GGT (301 IU/L), with high total bilirubin (392 µmol/L; direct bilirubin level: 345 µmol/L), and thrombocytopenia (119×10^9/L); C-reactive protein was markedly elevated (41.6 mg/L). HAV, HCV, and HIV were excluded. Serologic markers of previous CMV, EBV, and T. gondii infections were positive. Abdominal ultrasound showed known macronodular liver cirrhosis with manifest splenorenal shunting and splenomegaly. Anti-HEV IgM (165.9 IU/mL) and IgG (212.6 IU/mL) antibodies were positive. To exclude acute HBV-associated liver failure, polymerase chain reaction testing was performed using a commercially available kit (Abbott Laboratories, USA) to detect HBV-DNA (<12.5 IU/mL). HEV RNA was detected (9.76×10^5 copies/mL), and sequencing revealed HEV genotype 3f. Due to the severity of his condition, the patient was immediately transferred and underwent a high-urgency liver transplantation (CMV-positive transplant). The patient experienced the following complications: an ischemic cerebrovascular accident, acute renal failure, corticoid-induced diabetes mellitus, and CMV reactivation one month post-transplant (plasma viral load: 1,493 IU/L).

In September 2013, the patient died as a result of cardiac deterioration. A possible route of transmission could not be proven. However, there was a history of recent consumption of insufficiently heated pork sausage. Furthermore, the patient was at increased risk of developing severe complications due to the preexisting chronic liver disease.

**Patient 3**

In June 2014, a 66-year-old Caucasian man was admitted for investigation of bilateral shoulder pain associated with remarkably dark urine. He revealed a ten-day history of general malaise, loss of appetite, anorexia, and an influenza-like syndrome with diffuse myalgia. The shoulder pain was evolutive, followed by progressive neurologic complaints, including muscular weakness and loss of force in the left hand accompanied by paresthesia of the fingers and dysesthesia of the palm of the hand. The patient reported a recent trip to Southeast Asia. Magnetic resonance imaging of the head and cervical spine showed no abnormalities, as did computed tomography of the thorax and abdomen. Liver function tests showed elevated ALT (188 IU/L), alkaline phosphatase (159 IU/L), total bilirubin (29.1 µmol/L), and GGT (814 IU/L). Serology was negative for CMV, EBV, HIV, HSV, VZV, T. gondii, parvovirus B19, and Coxiella burnetii. Serology for HBV was weakly positive for the core antibody (signal-to-cutoff ratio: 9.19), and negative for surface and envelope antigens and antibodies. Polymerase chain reaction for HBV was negative. Anti-HEV IgG (174 IU/mL) and IgM (137 IU/mL) were positive, although no serum HEV RNA could be detected at the time of diagnosis. Immunoblot analysis (RecomLine Hepatitis E IgG/IgM; Mikrogen GmbH) confirmed the presence of the antibody with high suspicion of a genotype 3 infection (no bands for genotype 1 visible). It is likely that cross-reactivity with acute HEV infection lead to a false-positive HB core antibody reactivity, which became undetectable during the convalescent phase of HEV infection. Electromyography confirmed bilateral (idiopathic) brachial plexopathy suggestive of Parsonage–Turner syndrome. Therefore, the patient was diagnosed with an acute HEV infection triggering a bilateral Parsonage–Turner syndrome.

The patient was managed conservatively with physical therapy and nonsteroidal anti-inflammatory drugs and opiates for pain relief, without any antiviral therapy. Neurologic signs and symptoms improved within two months, and laboratory parameters returned to values within the physiologic reference range within one month. The patient recovered completely after eight months of intensive revalidation exercise.

**Discussion**

HEV has typically been considered as an imported, travel-associated disease. However, sufficient evidence has been gathered indicating that it is neither rare nor limited to developing countries. The diagnosis of HEV infection in immunocompetent individuals is based upon the detection of specific anti-HEV IgG and/or IgM antibodies in serum. Anti-HEV IgM is detectable from the fourth day after disease onset and persists for up to 3–5 months, whereas anti-HEV IgG appears shortly after IgM with a peak concentration at approximately four weeks after onset of symptoms and
In nonendemic countries, prevention is more complex, because several possible infection routes exist. Hand hygiene is probably the best preventive action. As occasional cases of HEV infection appear to be acquired by a zoonotic route, other preventive measures (e.g., adequate heating procedures for pork and boar/deer meat) are also useful. Screening of donated blood is one way to prevent transmission through blood products, however its cost-effectiveness has not yet been determined.

**Conclusions**

These distinct clinical cases highlight the fact that HEV should be considered in the differential diagnosis of patients with unexplained hepatic disturbances (acute or chronic) with or without extrahepatic manifestations. Although first truly identified in 1983, our knowledge about HEV, the prevalence, mode of infection, and potential treatment possibilities has only evolved significantly over the last few years. The lack of well-established diagnostic criteria and the absence of specific antiviral drugs are two points to consider in the work-up of patients with disturbed liver enzymes. In actuality, a considerable number of auctochthonous infections likely remains undiagnosed for all the reasons discussed above.

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**Conflict of interest**

None.

**Author contributions**

Data analysis, research of the background literature on the cases, writing the first draft (SDK); discussions and analysis of the cases, writing the manuscript (MR).

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