Acute Hepatitis Associated With Autochthonous Hepatitis E Virus Infection—San Antonio, Texas, 2009

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Locally acquired hepatitis E infection is increasingly being observed in industrialized countries. We report 2 cases of autochthonous acute hepatitis E in the United States. Hepatitis E virus genotype 3a related to US-2 and swine hepatitis E virus strains was isolated from one of the patients, indicating potential food-borne or zoonotic transmission.

Hepatitis E virus (HEV) infection is a major cause of acute viral hepatitis worldwide. In developing countries, it presents as both epidemic and sporadic hepatitis that is mainly associated with fecally contaminated drinking water [1]. Traditionally, HEV infections in industrialized countries have been associated with travel to regions of endemicity; however, recently, locally acquired cases of HEV infection are increasingly being observed in Europe and Japan [2, 3]. The specific sources of these autochthonous infections remain largely unknown. In the United States, 5 cases of autochthonous acute hepatitis E have been reported to date [4–7], but no clear source of infection was identified despite extensive investigation.

In September 2009, 2 unrelated patients with no recent travel history presented with signs and symptoms of acute hepatitis to the same hospital in San Antonio, Texas. Both patients had serologic evidence of HEV infection. We describe the clinical presentation of the patients and the investigation to determine the source of infection.

METHODS

Epidemiologic Investigation

We reviewed medical records and conducted interviews to identify possible exposures to HEV from 2 weeks through 3 months before onset of illness. Information sought included travel history, drinking water and food sources, exposure to animals, social contacts, and pre-existing medical conditions. Households and close contacts were interviewed to identify additional cases and determine potential risk factors for HEV infection. In addition, because one patient was a nurse’s aide at 2 nursing homes, we reviewed the medical records of nursing home residents for whom she provided care to determine whether transmission of HEV could have occurred in that setting.

Hepatitis E Testing

Serum specimens from case patients and their contacts were tested for anti-HEV IgM and IgG with use of enzyme immunoassays (Diagnostics Systems) performed according to the manufacturer’s instructions. Stool and serum samples from persons with a positive anti-HEV IgM were tested for HEV RNA with use of reverse-transcriptase polymerase chain reaction. The primers and amplification conditions have been described elsewhere [8]. The resulting 282 base-pair product from open reading frame 1 of the HEV genome was genotyped using nucleotide sequencing.

RESULTS

Case Patient 1

A 21-year-old Hispanic woman was admitted to the hospital on 3 September 2009 because of progressively worsening nausea, vomiting, and right upper quadrant abdominal pain of 1.5 months duration. She denied jaundice, fever, pruritus, and diarrhea but noticed dark urine 1 week before hospitalization. The patient reported a positive home pregnancy test result in July 2009 and passing a blood clot associated with abdominal cramping and vaginal bleedng 1 week before her admission; the serum pregnancy test result at admission was negative. During physical examination, she had icteric sclera and mild right upper quadrant tenderness but no hepatomegaly. At admission, her hemoglobin level was 13.9 gm/dL, her hematocrit was 41.5%, and her platelet level was 212,000
platelets/µL. Findings of liver function tests were as follows: alanine aminotransferase level, 1316 IU/L; aspartate aminotransferase level, 1105 IU/L; and alkaline phosphatase level, 247 IU/L. During hospitalization, her ammonia and bilirubin levels and International Normalized Ratio continued to increase to 151 µmol/L, 21.1 mg/dL, and 8, respectively. She tested seronegative for antibody to hepatitis A virus IgM, hepatitis B surface antigen, antibody to hepatitis B IgM, antibody to hepatitis B surface antigen, antibody to hepatitis C virus, and hepatitis C virus RNA but tested positive for anti-HEV IgM and IgG, with signal-to-cut-off ratios of 2.2 and 1.6, respectively. HEV RNA was not detectable in serum or stool specimens despite repeat testing. Two weeks after admission, anti-HEV IgM and IgG signal-to-cut-off ratios were 2.2 and 1.5, respectively. Liver biopsy showed severe hepatitis with foci of confluenence and no evidence of chronic hepatocellular disease. Autoimmune hepatitis, herpesvirus, and Epstein-barr virus infections; Wilson disease; hemochromatosis; and acetaminophen toxicity were ruled out. The case patient progressed to fulminant liver failure, and she died 1 month after admission.

Information on exposure was obtained from household members who reported that the patient drank alcohol heavily from May through July 2009. She had no history of travel or contact with travelers. She usually ate well-cooked pork meat and never ate game meat or pork liver. She ate raw oysters in July 2009. She always drank bottled water. She had 5 dogs and a cat in her house, and rodents were seen outside her house.

**Case Patient 2**

A 44-year-old Hispanic woman presented on 3 September 2009 to the same hospital as case patient 1 because of jaundice, dark urine, and pruritus of 1 week duration. She denied nausea, vomiting, abdominal pain, diarrhea, or fever. Physical examination was unremarkable except for icteric sclera. At admission, the patient’s liver enzyme levels were elevated (alanine aminotransferase level, 1004 IU/L; aspartate aminotransferase level, 2100 IU/L; alkaline phosphatase level, 476 IU/L; and bilirubin level, 24.9 mg/dL). Liver biopsy showed evidence of severe hepatitis with centrilobular necrosis. The lobular parenchyma showed extensive ballooning of hepatocytes with mild mixed macro- and micro-vesicular steatosis. The patient tested seropositive for total antibody to hepatitis A virus and antibody to hepatitis B surface antigen but negative for antibody to hepatitis A virus IgM, hepatitis B surface antigen, total antibody to hepatitis B, antibody to hepatitis C virus, and hepatitis C virus RNA. Additional testing ruled out cytomegalovirus and herpesvirus infections, syphilis, autoimmune hepatitis, Wilson disease, and acetaminophen toxicity. The patient tested positive for anti-HEV IgM and IgG with signal to cut-off ratios of 2.6 and 3.7, respectively. HEV RNA was detected in the stool sample, and sequencing studies showed HEV genotype 3a with 92.9% and 85.7% homology to the HEV US-2 strain and the swine HEV strain (GenBank accession no: AF060669 and AF082843), respectively (Figure 1). The patient’s liver function test results started to normalize by the middle of September. Anti-HEV IgM and IgG signal-to-cut-off ratios of 3.1 and 3.7, respectively, were obtained 2 weeks after admission. She reported no travel or contact with travelers. The patient drank treated municipal or bottled water and denied eating uncooked meat. She rarely consumed well-cooked pork meat and never consumed pork liver. She did not have any pet or wild animal contact, and environmental inspection of the area did not detect any significant findings. Family members reported that the patient had a history of cocaine use and heavy drinking. Case patient 2 lived ~10 km from case patient 1 in a suburban neighborhood of San Antonio, Texas, but had no identified relationship with case patient 1.

**Investigation of Contacts**

None of the 13 contacts of the 2 case patients experienced symptoms suggestive of acute hepatitis from April through November 2009. All tested seronegative for anti-HEV IgM and IgG.

Review of 100 medical records at the nursing homes where case patient 2 worked revealed 5 persons with elevated liver enzyme levels or symptoms suggestive of liver disease from April through November 2009. Three of the 5 persons agreed to be tested; 1 resident was found to be seropositive for anti-HEV IgG but negative for IgM.

**DISCUSSION**

We report 2 patients with autochthonous acute hepatitis E who were admitted simultaneously to the same hospital in the United States. Such clustering of cases initially suggested an outbreak of HEV infection; however, the investigation could not identify any link between the patients or exposure to a common source. Similar to the 5 previously reported autochthonous HEV infection cases in the United States [4–7], the investigation failed to identify a clear source of infection.

The source of HEV infection remains unidentified in the majority of sporadic HEV infections both in developed and developing countries, although gathering evidence suggests zoonotic transmission from the consumption of raw or inadequately cooked boar meat, venison, and porcine offal [9]. In the United States, evidence of zoonotic infection remains circumstantial, owing to close similarity in HEV genotype 3 strains infecting humans and swine [4, 6, 7] and the high HEV RNA detection rate (11%) in a study of packaged commercial pig livers in US groceries [10]; however, to date, no direct evidence [2] for swine-human transmission has been found.

For case patient 1, laboratory diagnosis was based on the detection of IgM and IgG anti-HEV. HEV RNA was not detected...
in this patient; this could be because of low viral titers not detectable by conventional polymerase chain reaction. Furthermore, in HEV infection, viremia is usually short-lived and can be detected for up to 10 days only after the onset of disease. However, HEV isolates from case patient 2 belonged to genotype 3a and were closely related to US swine HEV strains, suggesting that case patient 2 could have been infected by swine HEV. Nonetheless, both case patients denied eating raw animal meat. However, case patient 1 admitted to eating raw oysters 2 months before illness. This activity could have been a risk factor for her acquisition of hepatitis E in light of a recent outbreak of genotype 3 HEV infection that occurred on a cruise ship [11].

To our knowledge, this report presents the first fatal autochthonous hepatitis E in the United States. The young age of case patient 1 is also notable, considering that previous cases reported in the United States were in significantly older patients (age range, 43–69 years) [4–7]. In developing countries, HEV infection has been associated with mortality rates as high as 30% among pregnant women [1]. Although pregnancy could not be ascertained in case patient 1 at hospital admission, her reports of a positive pregnancy test result and vaginal bleeding and passing of blood clots 1 week before admission may suggest pregnancy that resulted in spontaneous abortion. Although the exact mechanism of liver injury in pregnancy remains unknown, fulminant hepatic failure could be related to a combination of immunologic, hormonal, genetic, and environmental factors [12]. Furthermore, the patient also had a history of heavy alcohol consumption. Excess alcohol consumption could compromise hepatic function and predispose to symptomatic HEV infection [2, 11]. These factors likely contributed to her proclivity to fulminant hepatitis despite her young age.
Several challenges were faced in this investigation. The long duration from infection to the investigation could have contributed to recall bias of food items consumed during the infection period and hindered any collection of food samples dating back to that time for HEV testing. In addition, a major challenge for HEV diagnostic testing in the United States is the varying sensitivities and specificities of current commercially available tests [13] that are not yet approved by the US Food and Drug Administration and developed for use in countries with high rates of HEV infections, where HEV genotypes other than genotype 3 predominate; this hinders adequate standardization and ascertainment of infection. Although a recent publication indicated a 21% prevalence of HEV infection in the United States [14], case reports of autochthonous hepatitis E remain limited in the United States, compared with other industrialized countries. This discrepancy might be explained by the combination of unavailability of US Food and Drug Administration–approved tests, not including hepatitis E in the testing panel, and physician unawareness of the potential local transmission of HEV.

In conclusion, this report describes 2 unrelated patients with autochthonous hepatitis E in the United States. The sources and routes of their infection could not be determined despite extensive investigation. Health care providers should consider HEV infection in patients with unexplained hepatitis, even in the absence of travel history.

Notes

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